Propagating Humanized BLT Mice for the Study of Human Immunology and Immunotherapy.

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Public Summary:
The humanized bone marrow-liver-thymus (BLT) mouse model harbors a nearly complete human immune system, therefore providing a powerful tool to study human immunology and immunotherapy. However, its application is greatly limited by the restricted supply of human CD34+ hematopoietic stem cells and fetal thymus tissues that are needed to generate these mice. The restriction is especially significant for the study of human immune systems with special genetic traits, such as certain human leukocyte antigen (HLA) haplotypes or monogene deficiencies. To circumvent this critical limitation, we have developed a method to quickly propagate established BLT mice. Through secondary transfer of bone marrow cells and human thymus implants from BLT mice into NSG (NOD/SCID/IL-2Rgamma-/-) recipient mice, we were able to expand one primary BLT mouse into a colony of 4-5 proBLT (propagated BLT) mice in 6-8 weeks. These proBLT mice reconstituted human immune cells, including T cells, at levels comparable to those of their primary BLT donor mouse. They also faithfully inherited the human immune cell genetic traits from their donor BLT mouse, such as the HLA-A2 haplotype that is of special interest for studying HLA-A2-restricted human T cell immunotherapies. Moreover, an EGFP reporter gene engineered into the human immune system was stably passed from BLT to proBLT mice, making proBLT mice suitable for studying human immune cell gene therapy. This method provides an opportunity to overcome a critical hurdle to utilizing the BLT humanized mouse model and enables its more widespread use as a valuable preclinical research tool.

Scientific Abstract:
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